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Multiple Myeloma Associated With Serum Amino Acid Disturbance and High Output Cardiac Failure

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We experienced a plasma cell leukemia (PCL) patient complicated with high output cardiac failure (HOCF), proved as his elevated cardiac index and pulmonary artery wedge pressure and decreased systemic vascular resistance index in a hemodynamic study. We found no possible causes of HOCF. Interestingly, HOCF was improved as PCL responded to intensive chemotherapy. On the other hand, he showed consciousness disturbance, and had frequent attacks of generalized seizure. His electroencephalogram showed slow waves, and a spike and wave complex. Hyperammonemia and abnormal amino acid distribution were also found. This abnormal serum amino acid distribution, especially elevated glycine level, was different from that seen in chronic liver failure, and he had no hepatic disease. After intensive chemotherapy, the serum ammonia level and glycine level decreased. In this patient, PCL seemed to be responsible for HOCF, hyperammonemia, and abnormal amino acid distribution. We experienced two more cases of multiple myeloma (MM) with HOCF, hyperammonemia, abnormal serum amino acid distribution, and consciousness disturbance of unknown origin. Those two cases showed slow waves in the electroencephalogram. Improvement was seen in their HOCF, hyperammonemia, and abnormal amino acid levels after chemotherapy. The possibility of MM as a cause of HOCF is discussed. Am. J. Hematol. 57:77–81, 1998. © 1998 Wiley-Liss, Inc.

Key words: multiple myeloma; plasma cell leukemia; high output cardiac failure; hyperammonemia; amino acid disturbance

INTRODUCTION

Although plasma cell leukemia (PCL) and multiple myeloma (MM) are well-known disease, there are few reports about the association between MM and high output cardiac failure (HOCF). Tamir et al. reported a PCL patient with HOCF [1]. Wade reported three similar cases [2]. These patients did not have any diseases known to cause HOCF, such as severe anemia [3,4], sepsis, hyperthyroidism, thiamin deficiency, arteriovenous shunt, and bone Paget disease [5]. Wade et al. found approximately 24% of randomly selected MM patients had a cardiac index of more than 4.0 L/min/m^2 in a cardiac ultrasonographic study [6].

On the other hand, we have reported that hyperammonemia and abnormal serum amino acid distribution are not so rare in MM patients and are different from those seen in patients with chronic liver failure [7,8]. The glycine level in MM patients is significantly higher than that in patients with hepatic failure and the tyrosine level in MM patients is significantly lower than those in patients with hepatic failure. Recently, we found that some of the patients with MM had both abnormal amino acid distribution and HOCF showing improvement after chemotherapy. The association between HOCF and MM is discussed.

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TABLE I. Laboratory Data of Three Cases

	Normal range	Case 1	Case 2	Case 3
Hemogram				
WBC (/μl) (plasma cell, %)	4,000–8,000 (0)	6,600 (23)	19,300 (80)	3,200 (0)
Hb (g/dl)	12–18	9.3	8.8	7.0
Platelets ($\times 10^4$/μl)	13–32	3.5	19.8	8.9
Bone marrow				
Plasma cell (%)	<0.8	Dry tap	80.0	59.2
Blood chemistry				
T-Pr (g/dl)	6.5–8.1	7.0	8.0	9.3
M-protein (g)	0	—	2.4	5.2
GOT (U/L)	8–32	35	60	14
GPT (U/L)	6–38	25	67	8
LDH (U/L)	236–427	435	363	273
Ammonia (μg/dl)	16–62	180	128	60
Free T_4 (ng/dl)	0.9–1.9	0.8	NT*	0.7
IgG (mg/dl)	950–1,950	691	552	264
IgA (mg/dl)	80–440	53	2,590	7,393
IgM (mg/dl)	40–280	25	20	<7.0
Serum amino acid (nmol/ml)				
Gly	180–310	586	803	1,026
Val	146–328	117	115	413
Ileu	30–94	35	37	124
Leu	60–146	58	69	208
Tyr	32–84	19	61	159
Phe	45–81	63	81	140

*NT, not tested.

CASE REPORT

Case 1

A 23-year-old man, who had a history of epilepsy after head injury at the age of 13, visited a hospital because of general fatigue and dyspnea. He was diagnosed with MM complicated with cardiac failure and was transferred to our hospital. Table I shows his laboratory data. Mild anemia, suppression of normal component of immunoglobulin, urine Bence Jones protein, elevated serum lactate dehydrogenase (LDH), and serum creatinine were found. His peripheral blood contained 23% plasma cells. Bone marrow biopsy showed myelofibrosis. The cardiac echogram demonstrated an enlarged of right atrium and no arterio-venous shunt, and the abdominal ultrasonographic study demonstrated hepato-splenomegaly and dilated inferior venae cavae. We diagnosed him with PCL complicated with right cardiac failure. Chest Xp (Fig. 1) indicates that his cardio-thoracic ratio was 67.7% and pulmonary artery dilatation was enhanced. Laboratory data revealed that he had no severe anemia, sepsis, or hyperthyroidism. He showed somnolence and his electroencephalogram showed slow waves, and a spike and wave complex. He had frequent attacks of generalized seizure during his clinical course. Although he had no hepatic disease, hyperammonemia and abnormal amino acid distribution, especially hyperglycinemia, were found (Table I). As he had cardiac failure and renal failure at his admission, and was gradually exacerbated, hemodialysis and intensive chemotherapy were started

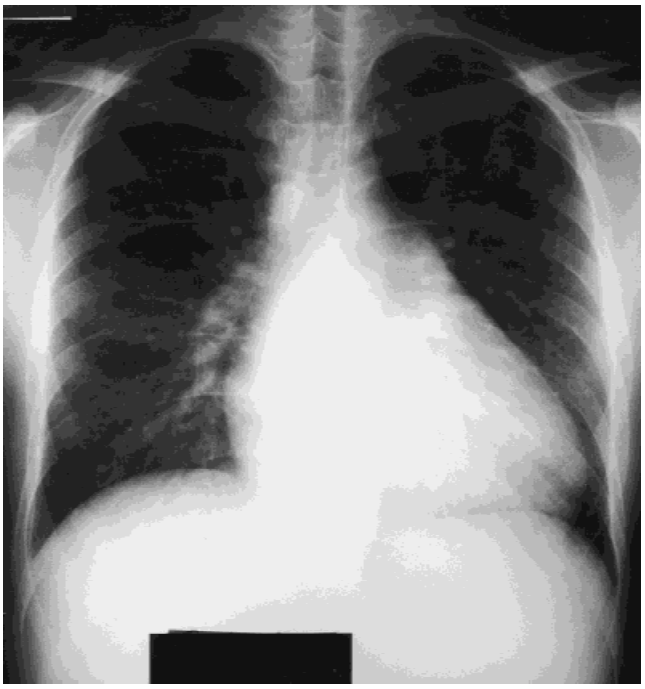

Fig. 1. Chest roentgenogram of case 1 on admission.

(Fig. 2A). Table II shows the hemodynamic studies performed at day 7, 8, 9, and 34. After two courses of chemotherapy, the serum levels of lactate dehydrogenase (LDH), ammonia, and glycine and cardiac index showed improvement but systemic vascular resistance remained

TABLE II. Hemodynamic Study of Three Cases

	Normal range	Case 1				Case 2	Case 3
		Day 7	Day 8	Day 9	Day 34		
Cardiac index (l/min/m^2)	2.5–4.0	11.6	6.2	7.3	5.3	6.3	5.3
Pulmonary capillary wedge pressure (mmHg)	7–13	15	15	8	7	30	17
Pulmonary artery mean pressure (mmHg)	1–10	27	24	15	15	40	36
Systemic venous resistance index (dynes.sec.$cm.^5$ m^2)	1,500–2,000	559	948	643	697	573	1,404

to be low on his 34th hospital day (Table II). His consciousness level improved to an alert state and his renal function was recovered after chemotherapy. He was discharged and entered a plateau phase with maintenance chemotherapy for 489 days. Finally, he became resistant to chemotherapy with increase in both serum level of ammonia and glycine. He died of respiratory distress on his 713rd day after diagnosis (Fig. 2A). Autopsy revealed almost normal liver histology (data not shown).

Case 2

A 44-year-old man visited a hospital because of chest oppression on inspiration, cough, and weight loss (6 kg during 6 months). His chest roentgenogram revealed enlargement of cardiac configuration and pleural effusion on the right side. A cardiac ultrasonographic study demonstrated enlargement of right atrium and inferior venae cavae. Table I shows his laboratory data. Anemia, leukocytosis with 80% plasma cells, suppression of normal immunoglobulin component, serum M-protein (IgA-λ), and urine Bence Jones protein were found. He was diagnosed with PCL. Although he showed slightly elevated liver enzymes and hyperammonemia, the pattern of amino acid distribution, especially high level of serum glycine was different from that in hepatic diseases (Table I). His thoracentesis specimen showed abundance of plasma cells. As in case 1, his cardiac index was increased and systemic vascular resistance index was decreased (Table II). He showed somnolence in his clinical course and his electroencephalogram showed slow waves. After two courses of chemotherapy, his right cardiac failure showed improvement, his pleural effusion diminished, and serum ammonia level decreased to almost normal level (Fig. 2B). When PCL exacerbated, his serum levels of ammonia and glycine were elevated again. Despite intensive chemotherapy, he died of respiratory distress on his 380th day after diagnosis. No obvious causes of HOCF and hyperammonemia were revealed by autopsy although slight plasma cell infiltration in the liver and lung was found.

Case 3

A 65-year-old woman with MM who had been treated for 3 years was readmitted to our hospital because of complaint of dyspnea and soft tissue mass, which was considered to be a plasmacytoma located on the right side of the chest wall. Her chest roentgenogram demonstrated pleural effusion and cardiac ultrasonography showed enlarged left atrium probably because of prolapsed mitral valve. Thoracentesis of pleural effusion showed that her effusion was exudative. Anemia, thrombocytopenia, and a high level of serum M-protein were found (Table I). Pulmonary artery catheter examination showed HOCF, e.g., elevated cardiac index and pulmonary capillary wedge pressure, and decreased systemic vascular resistance index (Table II). However, we could not find any causes of HOCF. She showed somnolence in her clinical course and slow waves on her electroencephalogram. She had a high level of glycine and ammonia although her liver function was normal. After intensive chemotherapy and radiation therapy were started, the serum level of both glycine and ammonia started to decrease (Fig. 2C). However, as she became resistant to the therapy, the serum level of ammonia gradually elevated. She died of bacterial pneumonia on her 111st hospital day. Autopsy revealed slightly perivascular deposition of AL amyloid in lungs, liver, spleen, pancreas, and bladder, which was not a cause of organ failure.

DISCUSSION

We have experienced three MM patients with HOCF, hyperammonemia, and abnormal amino acid distribution, especially hyperglycinemia. They did not have severe anemia, sepsis, thyroid diseases, arterio-venous shunt, or thiamin deficiency, which may cause HOCF. In case 1, repeated hemodynamic study demonstrated that cardiac index decreased with the improvement of PCL.

Tamir et al. reported a case of PCL with HOCF show-

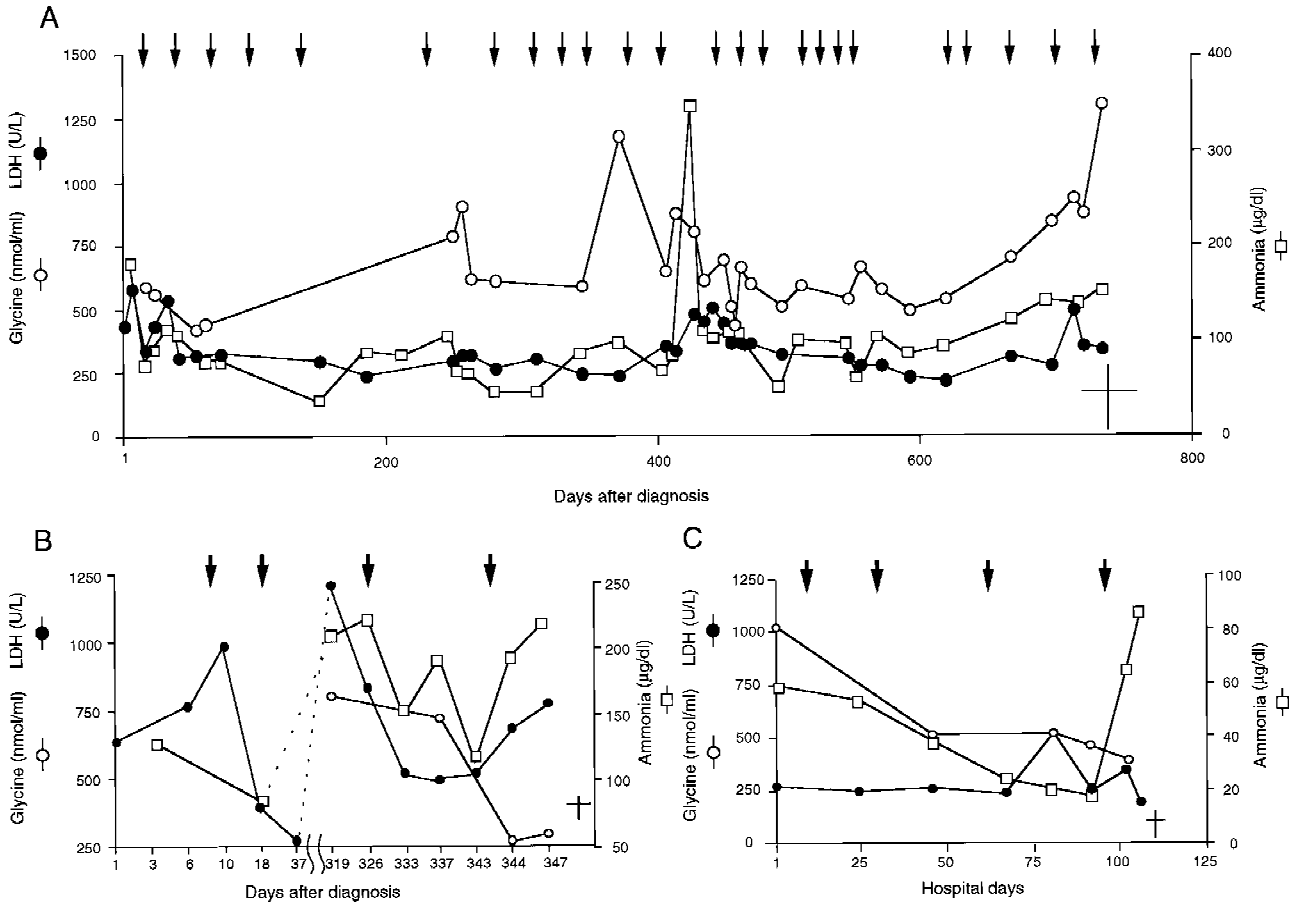

Fig. 2. Clinical courses of case 1 (A), 2 (B), and 3 (C). Each arrow represents chemotherapy such as melphalan, cyclophosphamide, vincristine, and predonisolone.

ing improvement of HOCF after chemotherapy [1]. In 1988, Wade et al. reported three MM patients complicated with HOCF [2]. None of them had any other diseases known to cause HOCF. They also found eight patients with a cardiac index of more than 4.0 L/min/m^2 in a cardiac ultrasonographic study of 34 randomly selected MM patients by the pulse doppler method [6]. These studies suggest that the complication of MM or PCL with HOCF is not so rare. Increase of circulating plasma volume due to hyperviscosity could be a cause of HOCF. However, this possibility could be excluded in case 1 since the amount of M-protein in serum was not high because of Bence Jones type myeloma. Therefore, we speculate that some unknown substance released from plasma cells dilated their peripheral vessels. The decrease of systemic venous resistance may be a unique character of HOCF in MM.

These three patients showed somnolence and slow waves in their electroencephalogram with disease progression. Hyperammonemia and abnormal serum amino acid distribution, especially a high level of glycine were commonly found. These abnormal findings correlated with the disease status. We reported that the abnormal amino acid distribution in MM patients with hyperammonemia is different from that seen in chronic liver failure. The glycine level was significantly higher in MM patients, but the tyrosine level was significantly higher in the chronic liver failure patients [8]. Microscopic evaluation of the patient's liver indicated that they did not have diffuse hepatic disease causing hyperammonemia or abnormal serum amino acids distribution. These findings suggest that the hyperammonemia and abnormal serum amino acid distribution are correlated with malignant plasma cells. This was also confirmed by the observation that abnormal amino acid distribution and HOCF showed improvement along with the improvement of MM.

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